REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-9, 12-33, 35-38 and 42-78 are in the case and are before the Examiner.

I. The Amendments

Claims 1, 18, 42, 47, 51, 63, 75, and 78 have been amended to add the word "corresponding" and to delete the phrase "as compared". Support for these amendments can be found in paragraphs [0055] and [0152] through [0156] of published application 20030138769.

II. The Action

A. Trademark Usage in Specification

Although the Action suggested that each letter of the various trademarks noted in the specification should be capitalized wherever they appeared, the alternative course of action done throughout the specification, highlighting of trademarks by including a proper trademark symbol, such as ™ or ® following the trademark word, is also acceptable (MPEP, section 608.01v, P6.20 Trademarks and Their Use, Examiner's Note).

B. Rejections Under 35 USC §112, First Paragraph

Claims 1-9, 12-33, 35-38 and 42-78 were rejected under 35 USC §112, first paragraph, because the specification while being enabling for a HBc chimer of SEQ ID NO:246-251 does not reasonably provide enablement for a HBc chimer containing up to

about 5% substituted amino acid residues in the HBc SEQ ID NO:246-251.

In order to overcome this rejection, the claims have been amended to clearly state that the amino acid substitutions in the chimer are conservative, thereby preserving the structural and functional integrity of the molecule. Specific support for these amendments can be found in the specification as detailed below.

Notably, the MPEP (8th revision) states in section 2163, page 175;

> "While there is no *in haec* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure."

It shall be first mentioned that in the "Definitions" section of the present application, on page 5, par [0055];

> "The term 'corresponds' in its various grammatical forms as used in relation to peptide sequences means the peptide sequence described plus or minus up to three amino acid residues at either or both of the amino- and carboxy-termini and containing only *conservative* (emphasis added) substitutions in particular amino acid residues along the polypeptide sequence."

Furthermore, in paragraph [0152] of page 15, the specification relates that:

> "a contemplated chimer molecule can also contain *conservative* (emphasis added) substitutions in the amino acid residues that constitute HBC domains I, II, III, and IV".

In addition, paragraph [0153] of page 15, the specification relates:

> "Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological activity or particle formation can be found using computer programs well known in the

art, for example, LASERGENE software (DNASTAR Inc., Madison, Wis.)."

Also, in paragraph [0155] on page 15 of the specification, it is stated;

"When the HBc portion of a chimer molecule of the present invention as above described has other than a sequence of a mammalian HBc molecule corresponding to positions 1 through 149, no more than about 20 percent of the amino acid residues are substituted as compared to SEQ ID NO:247 from position 1 through 149. It is preferred that no more than about 10 percent, and more preferably no more than about 5 percent, and most preferably no more than about 3 percent of the amino acid residues are substituted as compared to SEQ ID NO:247 from position 1 through 149."

Still further, paragraph [0156] on page 15 of the specification states:

"Substitutions, other than in the immunodominant loop of Domain II or at the termini, are preferably in the non-helical portions of the chimer molecule and are typically between residues 1 to about 15 and residues 24 to about 50 to help assure particle formation. See Koschel et al., (1999) *J. Virol.*, 73(3): 2153-2160."

Indeed, these passages illustrate that the specification enables chimeric HBc molecules with conservative amino acid substitutions that retain biological activity and structural integrity. Based upon these passages, one of skill in the art would be able to make such HBc chimers. The specification points out that the amino acid substitutions are to be up to 5 percent of the sequence, that the substitutions are to be conservative, that guidance as to proper substitutions can be obtained through LASERGENE software and the like, and that the region of substitution is in the non-helical portion of the molecule, within residues 2-15 and 24-50, to assure particle formation.

Therefore, it is respectfully requested that this rejection be withdrawn.

C. Rejection Under 35 USC §103(a)

Pumpens In View Of Zlotnick

Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 have been rejected as allegedly obvious over the disclosures of Pumpens (1995) in view of Zlotnick. This rejection is again respectfully traversed as discussed below.

First, the statement that all basic structural feature limitations of the HBc chimer are taught or suggested by Zlotnick and Pumpens cannot be agreed with. The Zlotnick paper is lacking adequate controls needed to reach the conclusion that a C-terminal cysteine stabilizes HBcΔ. One of skill in the art would realize this.

The Action suggests that Zlotnick teaches that Cp*150 is more stable than the other molecules that Zlotnick made, namely, Cp149 and Cp*149. Cp149 is the 149-mer capsid protein. Cp*149 is the 149-mer capsid protein with the cysteines at positions 47, 61, and 107 mutated to alanine. Cp*150 is the 150-mer capsid protein with the cysteines at positions 47, 61, and 107 mutated to alanine and the C-terminal arginine mutated to cysteine. In order to reasonably conclude that the C-terminal cysteine is the cause of the alleged added stability of the molecule, there must be an exact length molecule of the exact sequence with a different amino acid besides cysteine at the C-terminus to compare and contrast. Without such a control 150-mer capsid protein, it cannot be properly concluded that the C-terminal cysteine was the cause of the alleged stabilization of the molecule.

It is equally plausible that the removal and substitution of arginine with another amino acid at the C-

terminus of that molecule has led to increased stability of that molecule. It is conceivable that the terminal arginine is destabilizing to the molecule, in the absence of a proper control. Cp149 is not a proper control of Cp*150. The length is not the same. A proper control would be another Cp*150 where there is a conservative amino acid substitution at the C-terminus, such as lysine for arginine. A second essential control would be another Cp*150 where a non-conservative amino acid substitution at the C-terminus is made. These controls are essential to a believable argument that the alleged stabilization was due to the C-terminal cysteine and these controls are missing in the Zlotnick paper.

As such, it cannot be concluded by one of skill in the art, that the C-terminal cysteine substitution was responsible for alleged increased stabilization. It must be noted that Zlotnick was not looking for ways to increase stability of capsid particles and is probably why he chose not to issue such a conclusion without the studying the proper controls.

Also, the Action suggested that the citations of Zlotnick presented in the last response were incomplete. This statement is not agreed with. It cannot be denied that Zlotnick (page 9558, Results and Discussion) made the statement that:

> "Purified Cp*149 and Cp*150 assemble into capsids under the same conditions as other Cp constructs (10, 15), with or without DTT. These capsids were indistinguishable by negative staining electron microscopy and sedimentation on sucrose gradients (data not shown)."

This passage states that molecules without C-terminal cysteine (Cp*149) assemble into capsids *under the same conditions as other Cp constructs*, including Cp*150, which has the C-terminal cysteine. In other words, Zlotnick states that it makes no difference whether or not the capsid has a C-

terminal cysteine in terms of stability and assembling into capsids. Also, Zlotnick states that the capsids studied (i.e., Cp*150 with and Cp149 without C-terminal cysteine) were *indistinguishable*. This is the *first* statement Zlotnick makes in his Results and Discussion section, which one of skill in the art would appreciate as to importance.

Next the Action highlights several sentences from Zlotnick regarding disulfide bonding. Again, without the proper controls, it is impossible for one of skill in the art to believe the quoted statements of Zlotnick about allegedly stability. To reiterate, there is only a 150-mer C-terminal cysteine capsid protein and no 150-mer control capsid protein.

Lastly, Zlotnick states on page 9560, column two, first paragraph that:

> "Other observations imply that the C termini also may influence assembly in more subtle ways. For instance, binding Au11 to Cp*150 induces assembly, though Au11 cannot crosslink subunits nor, because of its organic shell, coordinate C-terminal cysteines. Binding Au11 may cause small changes in the molecular surfaces, near the C termini, that dock together when dimers polymerize and, in this way, stimulate the assembly process.

One of skill in the art would understand that Zlotnick suggests here that something besides cysteine binding is important in the assembly of capsid molecules. Zlotnick states that the data shows that Au cannot crosslink subunits nor coordinate C-terminal cysteines, yet the binding of Au11 to Cp*150 induces capsid assembly. Therefore, one of skill in the art would not conclude that C-terminal cysteines are responsible for capsid stabilization, but rather the opposite, that they are not that important. All in all, the Zlotnick manuscript is not valid as support of the premise that C-terminal cysteines enhance stability because it lacks proper controls and therefore

conclusions gleaned from it are suspect. Furthermore, Zlotnick himself suggests that other factors come into play regarding inducing capsid assembly and stability, such as changes in molecular surfaces.

Importantly, Zlotnick also teaches that neither of the cysteines at positions 48, 61, and 107 are vital for particle formation. His mutant where those cysteines were all replaced by alanines still formed particles identical to the native 183-mer particle. (see page 9558, column 2, paragraph 1).

As for Pumpens, the Applicant agrees with the statement from a previous Action that Pumpens does not teach replacing one or both cysteines at position 48 and 107 by another residue and adding a C-terminal cysteine.

Therefore, because the combination of Zlotnick and Pumpens does not teach that the modification of positions 48 and 107 of HBc and the addition of a cysteine at the C-terminus would increase stability, it is respectfully requested that this rejection be withdrawn.

D. Second Rejection Under 35 USC §103(a)

Pumpens In View Of Zlotnick and Thornton

Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 were again rejected as allegedly obvious from the combined disclosures of Pumpens in view of Zlotnick as above, and further in view of Thornton et al. U.S. Patent No. 5,143,726. This rejection is again respectfully traversed as discussed below.

The deficiencies of the combined teachings of Pumpens and Zlotnick in the previous discussions above are hereby repeated.

In the last Action, it was said that the claims of Thorton specifically teach a polypeptide immunogen operatively linked by a peptide bond to N-terminal flanking sequence, or C-

terminal flanking sequence of HBc, or HBV core protein from about position 70 to about position 140 from the amino terminus thereof. This is a vague and overgeneralized statement. More specifically, in column 9, lines 59-63, Thorton states:

> "Thus, the present invention contemplates an immunogenic polypeptide conjugate comprising a HBcAg protein operativley linked though an amino acid residue side chain to a polypeptide immunogen".

In contrast, the present invention does not utilize an endogenous amino acid side chain for linking. The present invention utilizes a heterologous linker residue (see claim 12). Therefore, that which Thorton is teaching is different from that which is being used in the present application. Thus the rejection in view of Thorton with Pumpens and Zlotnick should be withdrawn.

E. Summary

Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By Gerald T. Shekleton
Gerald T. Shekleton, Reg. No. 27,466

HUSCH BLACKWELL SANDERS LLC WELSH & KATZ
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Attachments
Petition and Fee
RCE and fee